

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC23170A		FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/IB2004/004049		International filing date (day/month/year) 06.12.2004	Priority date (day/month/year) 17.12.2003	
International Patent Classification (IPC) or national classification and IPC A61K31/00, A61K31/427, A61K31/425, A61K31/4015, A61K31/4025, A61K31/566, A61P19/10				
Applicant PFIZER PRODUCTS INC. et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 17.01.2005		Date of completion of this report 09.11.2005		
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Greif, G Telephone No. +49 89 2399-		



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IB2004/004049

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-50 as originally filed

Claims, Numbers

1-14 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-14 (in parts)

because:

☒ the said international application, or the said claims Nos. 1-14 (with respect to IA only) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 1-11 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	
Inventive step (IS)	Yes: Claims	12-14
	No: Claims	1-11
Industrial applicability (IA)	Yes: Claims	1-11 (no opinion)
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
2. Claims 1-6 refer to a great number of possible compounds falling under the definitions of Formula I. Claims 1-8, 10 and 11 refer to a great number of possible estrogens.
Support for the claimed effect, however, is only given for a specific combination of claim 12.
Synergy is an unpredictable characteristic of a mixture, occurring under particular conditions (for example in a particular amount of the individual components) which must be proved by appropriate experimental results for each individual mixture. As far as the present application is concerned, it is thus only convincingly demonstrated for the combination of claim 12. It follows that the only claims supported by the description are claims 12-14.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
D1: US 2003/149086 A1
D4: ARRENBRECHT S ET AL: "Effects of transdermal estradiol delivered by a matrix patch on bone density in hysterectomized, postmenopausal women: a 2-year placebo-controlled trial." OSTEOPOROSIS INTERNATIONAL : A JOURNAL ESTABLISHED AS RESULT OF COOPERATION BETWEEN THE EUROPEAN FOUNDATION FOR OSTEOPOROSIS AND THE NATIONAL OSTEOPOROSIS FOUNDATION OF THE USA. 2002, vol. 13, no. 2, 2002,

pages 176-183

2. Novelty

D1 discloses compounds of formula I for the treatment of conditions with low bone mass, such as osteoporosis (claims), and also refers to methods for treating vertebrates with low bone mass with an amount of compound of formula I in combination with other active compounds, such as an estrogen agonist/antagonist as preferred combination (Paragraphs 64-113). Also disclosed are kits comprising the two classes of compounds. The specific compounds of claim 7 are also disclosed in claim 9 of D1.

The above-raised objections notwithstanding, claims 1-14 are novel over the prior art, since synergistic combinations are not disclosed.

3. Inventive Step

3.1. D2 discloses the anti-bone loss effect of 17-beta-estradiol (abstract). All compounds specifically claimed are thus shown in the prior art to have the claimed effect in the absence of any combination.

3.2. Considering the lack of experimental data over the breadth of the claims, claims 1-11 are not considered to be inventive, since it has not been shown by the applicant that this synergistic effect has been obtained with a convincing number of possible combinations.

The applicant is furthermore reminded that synergistic effects are not predictable and are, per definition, unexpected. Therefore, even if the applicant has shown a synergistic effect for a specific combination, this would not imply that other claimed combination for which no synergy has been shown, would be considered as involving an inventive step.

3.3. Inventive step can be acknowledged for claims 12-14, for which a synergistic effect has been shown.

4. Industrial applicability

For the assessment of the present claims 1-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for

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example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.